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Vincent T. DeVita, Jr.
Samuel Hellman
Steven A. Rosenberg
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Chapter 53

William A. Blattner
Robert N. Hoover

Cancer in the Immunosuppressed Host

Beginning in 1979, the epidemic of Kaposi's sarcoma, non-Hodgkin's lymphoma, and some other tumors in acquired immunodeficiency syndrome (AIDS) patients, has focused new attention on the role of immunosuppression in the etiology of cancer.[1-3] Thus it is timely to review the pattern of cancer occurrence in groups who are immunosuppressed by virtue of inborn, therapeutic, or acquired immunodeficiency states. Furthermore, with the recent recognition that a member of the human T-cell lymphotropic family of retroviruses, HTLV-III, is the likely cause of AIDS, new insights concerning this relationship are likely to emerge.[4]

The "immune surveillance" theory proposed by Thomas and Burnet hypothesized that, in all individuals, clones of neoplastic cells with new surface antigens arise repeatedly but are then rejected and eliminated by the cellular immune system of the host.[5,6] Whenever this system is impaired, cells may accumulate unchecked to form a malignant tumor. In the early 1970s this concept attracted considerable and widespread acceptance, but challenges have been raised on experimental, epidemiological, and clinical grounds.[7] In fact, while no general diathesis of malignancy has been observed among immunosuppressed groups, large excess risk of limited numbers of tumor types provides opportunity for defining etiologic mechanisms and anticipating types of tumors likely to arise in the group most recently defined at risk for immunodeficiency cancer, AIDS patients.

CONGENITAL IMMUNE DEFICIENCY

As outlined in Chapter 8, the functional secrets of various compartments of the immunologic system are starting to be unlocked. Rapid advances in immunology have defined the ontogeny of two major compartments of the immune system, T- and B-cells, and have dissected a myriad of subtypes of cells with capabilities for various regulatory functions.[8] Much of this understanding has come about through the study of congenital immunodeficiency syndromes, where developmental defects have resulted in ablation of one or another compartment of the immune system.[9]

To date, 14 such naturally occurring, genetically determined immunodeficiency diseases, with a variety of distinct clinical patterns and underlying defects, have been defined and associated with malignancy.[10] Seven of these syndromes, summarized in Table 53-1, account for the bulk of such immunodeficiency-associated malignancies. These conditions differ from one another as to the age of onset (birth to adulthood), the severity of immunodeficiency symptoms, the scope of cellular abnormalities, and the prognosis and pattern of malignancies. The most common cause of death for all of these syndromes is overwhelming infection with opportunistic infectious agents. Estimates of the overall cancer incidence for these syndromes vary from 1.7% to 4%, and the rate by syndrome category ranges from less than 1% to over 30%.[11]

In the most recent update of the immunodeficiency-cancer registry, a total of 267 confirmed malignancies were reviewed.[10] Non-Hodgkin's lymphomas accounted for over one half of the malignancies, with a significant number originating in unusual extranodal sites, including the brain and gastrointestinal tract. Among the limited number of these tumors that have been immunotyped, most are of B-cell origin.[12,13] An uneven distribution of other cancer types are distributed among the other syndromes.[10] In some respects, risks for malignancy are an inverse function of the severity of the

TABLE 53-1. Cancer in Congenital Immunodeficiency

SYNDROME	DEFECTS	RISK/ MEDIAN AGE	TUMORS*
Severe combined immunodeficiency (SCID)	Stem cell Affects B- and T-cells	1.5%/0.9	Leukemia, ALL, HD, NHL
DiGeorge	Thymic hypoplasia (isolated T-cell)	Ukn	NS
Ataxia telangiectasia	Complex developmental defect, Ig+ severe cellular/ humoral response with radiation DNA repair defect	12%/9	ALL, NHL, NS, Ov, Sk, St
Infantile sex-linked hypogammaglobulinemia (Bruton type)	Isolated B-cell defect	0.7%/3	ALL, NHL
Wiskott–Aldrich (immunodeficiency with thrombocytopenia and eczema)	Complex cellular and humoral autoimmunity	15–30%/6	NHL, AML
Common variable immunodeficiency	Complex cellular and humoral autoimmunity	2.5%/<16 8.5%/>16	NHL, St
X-linked lymphoproliferative syndrome	Defective humoral and cellular responses to EBV infection, resulting in immunoablation	35%/10	NHL

* ALL = acute lymphoblastic leukemia; HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; NS = nervous system; Ov = ovarian; Sk = epidermal; St = stomach; AML = acute myelogenous leukemia; Ig = immunoglobulin.

underlying immune deficiency (*i.e.*, the likelihood of developing malignancy is dependent, to some degree, on the length of survival of the at-risk individual.) Thus the more severe forms of immunodeficiency have low malignancy rates, presumably resulting from the relatively short survival of these severely compromised individuals who succumb to opportunistic infections prior to experiencing the risk for malignancy.

Underlying factors in addition to the immunodeficiency itself are also likely codeterminates of cancer risk observed in some of these syndromes. Thus in ataxia telangiectasia a defect in the repair of DNA damage due to gamma radiation may also contribute to the pathogenesis of the spectrum of malignancies seen in this disorder, while a complex bone marrow defect appears to underlie the predisposition of Wiskott–Aldrich syndrome patients to develop acute myeloid leukemia.[9,14] Autoimmune disorders have also been reported frequently in patients with combined variable immunodeficiency, perhaps accounting for the stomach cancer excess of this syndrome, due to immunologically induced atropic gastritis.[15] Impaired immune surveillance against primary Epstein–Barr virus infection in young men with an X-linked lymphoproliferative syndrome results in an uncontrolled B-cell lymphoproliferation that begins as a polyclonal B-cell expansion and terminates as a monoclonal B-cell immunoblastic lymphoma.[16] Impaired T-cell regulation of EBV-induced immunoproliferation in this syndrome provides a model for other immunodeficiency-associated B-cell neoplasms, such as found in AIDS patients and renal transplant patients.[16]

In addition to these clinically overt immunodeficiency states, a variety of reports suggest that clinically inapparent immunologic defects, detectable only by laboratory study, may also predispose to cancer risk. Cancer-prone families afford the opportunity to define these interrelationships. Familial aggregations of various lymphoproliferative diseases have documented a relationship of subtle immunodeficiency to primary lymphatic cancers, including CLL, Waldenstrom macroglobulinemia, Hodgkin's and non-Hodgkin's lymphoma, and acute lymphoblastic leukemia.[18–21] In some cases, this immune deficiency appears to be linked to major histocompatibility genes, which are known to regulate particularly T-cell-mediated immunologic responses, especially those mediated by T-cells.[8,19] This linkage may be shared in patients with clinical and subclinical autoimmune processes, again supporting the notion of altered T-cell immune regulation in immunodeficiency cancer.[18]

DRUG-INDUCED IMMUNODEFICIENCY

The best quantified evidence linking immune alteration to human carcinogenesis comes from studies of persons receiving kidney transplants and large doses of immunosuppressive agents to prevent rejection.[22–30] Numerous investigations have documented a substantial excess risk of non-Hodgkin's lymphoma in these populations.[22,23,25] The overall risk of this tumor is approximately 25 times to 60 times greater than expected.[22,23] This translates into an absolute excess of one to two cases of non-Hodgkin's lymphoma per 1000 transplant recipients per year. Two unusual features of this excess risk of lymphoma are noteworthy: The onset of risk is explosive, appearing within months of transplantation, and the anatomic distribution of the site of involvement of the lymphoma is highly unusual, presenting as primary lymphomas of the central nervous system in approximately half of the cases.[22,23] While for some time no meaningful variation in lymphoma risk was noted among subgroups of transplant recipients, differences have recently begun to emerge. Some studies of transplant recipients have shown a definite decline in the

lymphoma risk over time, in one study dropping from 2 per 1000 per year for those transplanted before 1968, to 1 per 1000 per year for those transplanted after 1971.[31] This same study, has also observed a direct association between increasing risk of lymphoma and increasing number of transplants, and an inverse association between risk and closeness of the relationship of the donor to recipient.[31] The lymphoma risk among those receiving a cadaver transplant was three times that of patients who received their graft from a sibling, a finding also supported by other studies.[29,32]

Recently concern has arisen over a particularly high lymphoma risk among transplant recipients receiving cyclosporin as an immunosuppressive drug.[33] This has been especially true of those receiving the drug in conjunction with cardiac transplants.[34,35] However, the most marked excess seems to have occurred among the first patients in whom the drug was investigated and in whom other immunosuppressive agents also were given. In these circumstances, the total immunosuppressive treatment could be considered excessive.[36] More recent experience in which cyclosporin at reduced doses is the sole initial immunosuppressive agent among kidney recipients, has not revealed any exaggerated risk of lymphoma, compared to the risk seen with other immunosuppressive drugs.[37] Most recently, an unusually high prevalence of lymphoid malignancies has been noted among primarily bone marrow transplant recipients whose marrow was depleted of certain T-cell populations using cytotoxic monoclonal antibodies to kill selected T-cells. If this risk is confirmed, it suggests that an induced immunologic imbalance resulting from this type of manipulation could be a cofactor in the lymphoma risk.[37]

Another type of tumor for which transplant recipients clearly experience an excess risk is squamous cell cancer of the skin.[22,24] An analysis of the skin cancer experience of the United States, the United Kingdom, and Australia indicates that squamous malignancy of the skin occurs at a rate 10 times to 20 times higher than expected.[23] This excess increases with duration of treatment. At the same time, no excess of basal cell cancers of the skin has been noted.

No across-the-board increase in cancer risk has been observed in this group, since several common tumors, such as those of the breast and large bowel, have not occurred excessively. Instead, increased risk has been limited to particular sites. Most noteworthy have been excesses of soft-tissue sarcoma, particularly Kaposi's sarcoma, primary malignancies of the liver and biliary tract, and malignant melanoma. With reference to Kaposi's sarcoma, this risk has been substantially less than that observed in AIDS patients, suggesting risk factors for this tumor that differ between these groups.[26] Some analyses, although not controlling for relevant lifestyle and exposure variables, have also suggested excess cancers of the lung, bladder, and thyroid as well as leukemia.[22,28]

Several conclusions concerning carcinogenic mechanisms seem appropriate, based on the cumulative experience of immunosuppressed transplant recipients. The excess of non-Hodgkin's lymphoma appears to result from mechanisms that could involve a role for oncogenic viruses, graft-versus-host reactions, or chronic antigenic stimulation. Epstein–Barr virus induced B-cell proliferation in a setting of altered T-lymphocyte regulation has been suggested by molecular analysis of transplant-associated tumors and by the reversibility of these lesions after withdrawal of immunosuppressive therapy or Acyclovir treatment.[16,38–40] In addition, the risk of this tumor is most apparent in those who are both immunosuppressed and antigenically stimulated, and the level of risk appears to be directly related to both the level of immunosuppression and the level of antigenic stimulation.[23,31] The transition of one such case from polyclonal to monoclonal expression supports such a multifactorial model.[40]

The excess of tumors other than lymphomas noted among transplant recipients may be due also to immunologic mechanisms, but probably is due to mechanisms other than those responsible for the lymphoma excess. Specific immunologic mechanisms have been suggested for malignant melanoma.[41] The excess of hepatobiliary malignancies may relate in some way to the high prevalence of infections with hepatitis B virus among transplant recipients.[16] However, some enhancement of the progression from antigenemia to clinical malignancy would have to be proposed for immunosuppressive therapy in order to explain the marked excess among transplant recipients compared to the currently unremarkable experience with respect to this tumor for dialysis patients who have a similarly high rate of infection with hepatitis B. Noteworthy among transplant recipients is the tendency for Kaposi's sarcoma to be a more important sequel of immunosuppressive therapy among ethnic groups known to be at high risk for this tumor.[26]

In terms of detection and prevention, the most obvious opportunities concern the excess risk of skin cancers, both squamous cell carcinoma and melanoma. Our knowledge of the etiology of these tumors, their high cure rates when detected early, the ease of screening for them, and the unusually aggressive nature of the cancers in immunosuppressed groups lead to a logical set of recommendations.[42–44] The groups at high risk should take measures to protect themselves from excessive exposure to sunlight and should routinely examine the skin of their entire bodies for growths, ulcerations, and changes in nevi. Physicians caring for such patients should also establish some routine of periodic examination for such changes. While there have been suggestions of excess risks of cancer of the uterine cervix among women in these groups, these have been difficult to substantiate because of a variety of methodologic difficulties.[27] However, since some concern exists, and since an easily applied screening tool exists, it would seem prudent to include periodic Pap smears among these recommendations. The current lack of effective screening tools for the other, relatively rare, tumors that are excessive in immunocompromised persons would argue against any more aggressive program of surveillance. A possible exception might be the selective addition of serum alpha-fetoprotein determinations among recipients at the highest risk of primary liver tumors. The treatment of cancer in the immune suppressed host is complex, by virtue of the fact that current therapies available for such treatment are immunosuppressive in their own right. There is considerable literature concerning this issue, particularly in the case of transplant recipients where immunosuppression is potentially reversible.[39]

A substantial body of evidence is emerging concerning the malignancy experience of patients treated with cytotoxic drugs, either for a first malignancy or for nonmalignant (*e.g.*,

rheumatologic) conditions.[7] Extensive evaluations of a variety of alkylating agents and anti-tumor antibiotics consistently find an apparent dose-related excess risk of primarily acute nonlymphocytic (ANLL) leukemia, presumably due to the clastogenic effects of these drugs.[45] These drugs are also profoundly immunosuppressive, which may contribute to the elevated risk of non-Hodgkin's lymphoma among patients treated with combination chemotherapy for Hodgkin's disease.[46] In this context it is noteworthy that the prevailing opinion about the pathogenesis of Hodgkin's disease involves an immunologic "civil war" between a patient's B-cells and T-cells that results in a considerable amount of antigenic stimulation in the context of underlying immunodeficiency, potentially amplified by cytotoxic drug therapy.[47]

CLINICAL CONDITIONS ASSOCIATED WITH ALTERED IMMUNITY

While profound states of immunosuppression can be the result of genetic conditions and some drug treatments, many more people have their immune systems altered by a variety of acquired clinical diseases than by genetic or drug considerations.[7] Some of these disorders with secondary immunologic defects have been associated with excesses of non-Hodgkin's lymphoma, similar to that seen among transplant recipients and patients with some genetic syndromes. The best documented examples are the excess risk of lymphoma experienced by patients with celiac disease (threefold to fourfold risk)[48] and those with sicca syndrome (40-fold risk).[49] These clinical conditions seem to identify a subgroup of patients with marked lymphoid reactivity, presumably from excessive antigenic stimulation, who are at particularly high risk for developing lymphoma.

Other groups sharing this pattern include African Burkitt's lymphoma cases, where a role of malarial-induced immunodepression and immunostimulation have been viewed as cofactors in the EBV-associated lymphoma.[7] Intestinal lymphangiectasia patients with cellular and humoral defects due to loss of protein and lymphocytes through dilated intestinal lymphatic channels also have an excess risk of lymphoma.

It should be noted that not all disorders that result in immunodeficiency and immunostimulation are clearly associated with an excess risk of lymphoma. For example, patients with Hansen's disease and those with systemic lupus erythematosus certainly do not experience an excess risk of lymphoma of anywhere near the magnitude experienced by transplant recipients or patients with the clinical conditions previously mentioned, if indeed they experience any excess risk at all.

Followup studies of patients with immunodeficiency due to tumors of the reticuloendothelial or lymphoid system document interesting patterns, including the excess risk of skin cancer in chronic lymphocytic leukemia (CLL) patients. An excess risk of malignant melanoma, lung cancer (particularly adenocarcinoma of the lung), and soft-tissue sarcomas, a pattern very similar to that among transplant recipients, is striking in this group.[50]

ACQUIRED IMMUNODEFICIENCY SYNDROME

CLINICAL AND EPIDEMIOLOGIC ASPECTS

The current epidemic of acquired immunodeficiency syndrome, first reported in 1981 in previously healthy homosexual men with Kaposi's sarcoma and opportunistic infections has riveted new attention on the mechanisms of immunodeficiency on the origins of cancer. As of February 1984, over 1000 cases of Kaposi's sarcoma, and another 2000 plus individuals with opportunistic infections, have been identified in the various AIDS risk groups. These cases do not include myriad other individuals with some signs and symptoms or subclinical markers of immunodeficiency who do not fit the strict CDC case definition, but who, nonetheless, represent a potential reservoir of persons at high risk for long-range sequelae, including malignancy.[51-54]

The major risk groups are summarized in Table 53-2, along with their reported malignancies. By far the largest risk group are homosexual and bisexual men, accounting for 76% of all AIDS cases. Intravenous drug users account for 15% of cases, and Haitian immigrants to the United States account for 4%.[55] This latter group, along with recent reports of AIDS in Haiti and more recently in Zaire, has fueled speculation on the historical connection between Kaposi's sarcoma, AIDS, and AIDS-like opportunistic infections in certain regions of Africa and the current United States epidemic.[56-58] The remainder, although constituting a small proportion of cases, are informative because they give clearcut clues to the role of a transmissible agent in the etiology of AIDS. This relationship is particularly clear in the handful of blood recipients where a single suspect donor has been identified.[59] Cases in the pediatric age group (children of prostitutes or i.v. drug users) suggest transplacental or perinatal exposure to the putative agent, while cases in sexual partners of AIDS patients (*e.g.*, spouses of i.v. drug users) provide evidence for venereal transmission, also linked in homosexual cases where certain sex practices (particularly anal receptive intercourse) have been linked to risk for AIDS-related immunologic abnormalities.[60] Thus the weight of epidemiologic evidence supports the hypothesis that a transmissible agent such as HTLV-III (see below) is responsible for inducing the underlying immunological perturbation that leads to the associated secondary outcomes of cancer and opportunistic infection.[4,52-54]

The nature of the induced immunologic defects in the syndrome is complex, but the most consistent abnormality is profound lymphopenia, particularly involving T-lymphocytes that bear the helper/inducer phenotype defined by the monoclonal antibodies OKT-4 or Leu-3.[61,62] This abnormality is manifest in vivo by anergy to recall or induced measures of cell-mediated immunity and in depressed in vitro response to virtually all measures of T-lymphocyte function.[62] Functionally the defect is most pronounced for T-cell effector functions involving helper/inducer cells, while suppressor/cytotoxic subpopulations appear to function normally. In addition, polyclonal B-cell activation, manifested by elevated IgG and IgA levels, and frequent occurrence of immune complex formation are common, and in vitro B-cells spontaneously secrete immunoglobulin. These activated B-cells are refractory to usual regulatory signals, suggesting an activated or trans-

TABLE 53-2. Cancer in Acquired Immunodeficiency Syndrome

RISK CATEGORY	PROPORTION OF AIDS (% OF FEMALES)	MALIGNANCY	MALIGNANCY RISK BY CATEGORY
Homosexuals/bisexuals	76.4% (0)	Kaposi's sarcoma	33%
		Lymphoproliferative	
		Non-Hodgkin's/ Burkitt's lymphoma	
		Hodgkin's disease	
		CLL	
		Squamous cell of the oropharynx	
		Cloacogenic carcinoma of the anus	
Intravenous (i.v.) drug users	14.8% (54.0%)	Unknown	Unknown
Haitians	3.9% (9.7%)	Kaposi's sarcoma	3%
Hemophiliacs	0.7% (0)	Burkitt's lymphoma	Unknown
Other	4.2% (36.3%)		
Blood recipients			
Zairians			
Infants of high-risk parents		Kaposi's sarcoma	
Female sex partners of AIDS patients		Kaposi's sarcoma	
Unknown			

formed phenotype that might play a role in the propensity to B-cell malignancy. [63] This complex of immunologic defects appears to arise from the cytopathic effects of HTLV-III on the helper/inducer subset of T-lymphocytes, resulting in a profound immunologic imbalance (see below).[64]

Clinical syndromes associated with AIDS reflect the effect of profound immunodeficiency. Thus a myriad of uncommon infectious complications, particularly *pneumocystis carinii* pneumonia, have been reported, as well as certain malignancies.[62] The chronic lymphadenopathy syndrome defined as unexplained adenopathy of 3 months duration or longer, without attributable cause, has been classified as an AIDS-related syndrome. Its relationship to clinical AIDS has been defined only recently through the common link of this disorder and AIDS to HTLV-III infection.[65,66] Other AIDS-related syndromes, including clinical conditions of persistent or refractory fungal or viral infection such as oral candidiasis or AIDS-like alterations in lymphocyte subsets, reflect an underlying immunological perturbation that is less severe than that of fullblown AIDS.[62] Finally, among groups at risk for AIDS, up to 20% or more have subclinical immunologic perturbations that may be markers of early AIDS or exposure to the cytopathic AIDS agent.[52-54] In support of the latter are epidemiological studies which suggest that these immunologic perturbations may be transmitted through contact involving persons from AIDS high-risk to low-risk areas. As a corollary, certain sex practices previously linked to AIDS risk are also associated with heightened risk for subclinical immunologic alterations.[52,54] The persistence of these immunologic alterations, their associaton with HTLV-III infection, and their link in some cases with a progression to frank AIDS, suggests that the pool of immunosuppressed individuals may be much larger than previously appreciated.[62] The long-range implications of this expanded at-risk pool to the occurrence and future risk for malignancies could be substantial.

The major form of AIDS-associated cancer, Kaposi's sarcoma, is seen in 34% of all AIDS patients.[2,62] Prior to the current epidemic, Kaposi's sarcoma was considered a rare disease in North America and Europe, even in immunosuppressed populations.[26] Recently their risk was quantified in the population based cancer registry in San Francisco, an AIDS high-risk area.[67] Prior to 1980 the rate was 0.2 cases per 100,000 population under age 50. Since 1980 the rate has soared to 8.50 cases per 100,000, a 30-fold jump attributable to the AIDS epidemic in this region. Clinically, in contrast to the usual form of relatively indolent disease, which occurs most commonly in elderly men of Italian or Jewish ancestry, the current form of disease is much more likely to be disseminated and clinically aggressive. In this regard the disease resembles the form of aggressive Kaposi's sarcoma previously reported to cluster in children, adolescents, and young adults in Central Africa, particularly in eastern Zaire, Uganda, and other countries of southern and central Africa.[68,69] It is noteworthy that these previously recognized African cases were found in the context of immunologic perturbation, not unlike that reported recently among AIDS patients with Kaposi's sarcoma.[70] With the discovery of AIDS-like immunocompromise in Zairian immigrants to Belgium, the link between this previously described cluster of Kaposi's sarcoma and the current AIDS epidemic has been strengthened, and a similar etiology has been postulated.[57] The recognition of this area as one endemic for HTLV-III infection supports this etiologic link (Gallo R: Unpublished data). The nature of the Kaposi's sarcoma malignant cell has been controversial but generally is linked to a cell of reticuloendothelial origin, although some authors have argued that generalized Kaposi's sarcoma is not a neoplasm at all but rather a multicentric proliferative lesion of endothelial origin.[71,72] A viral etiology has been postulated with a link to CMV infection, resulting in endothelial proliferation, uncontrolled in the milieu of immunocomprise.[16] However, it is also possible that HTLV-III itself, either directly or indirectly,

could be the underlying etiologic factor for Kaposi's sarcoma, since other groups with immunosuppression and CMV infection, particularly renal transplant patients, do not show anything near the magnitude of Kaposi's sarcoma risk that is clearly associated with AIDS.

Lymphoproliferative cancers, predominatly immunoblastic B-cell lymphoma, are the other major category of AIDS-related cancer, occurring in 3% to 4% of cases.[3,73] Cases of Hodgkin's disease, plasmacytoma, chronic lymphocytic leukemia, Burkitt's lymphoma, and occasionally T-cell non-Hodgkin's lymphoma, have also been reported in patients with or at risk for AIDS (see Table 53-2). In many respects these cases closely resemble those reported in patients with congenital or therapeutic immunodeficiency in whom extranodal or CNS presentation is frequent. The finding of persistent generalized lymphadenopathy prior to the development of frank lymphoma raises a question of the relationship of chronic adenopathy syndrome described above to subsequent lymphoma risk.[73] Of interest is the finding that the distinctive pattern of follicular hyperplasia seen in these lymphoma cases is sometimes identical to that of the chronic adenopathy syndrome in the eyes of some pathologists. The actual risk for lymphoma in AIDS patients or at-risk groups has not been quantified because of the difficulty of defining populations at risk. But the pattern of occurrence would suggest that risks are likely to approach those previously quantified in other immunosuppressed populations. With the availability of a test for HTLV-III exposure, it should be possible to better define the population at risk for lymphoma and provide this sort of quantitative risk estimate. The etiology of these AIDS-related lymphomas is unknown, but a role for EBV-induced lymphoproliferation in a setting of immunologic impairment has been postulated for congenitally and therapeutically immunosuppressed individuals.[16] In addition, a role for chronic antigenic stimulation or potential graft-versus-host-like disease, as reported in other high-risk populations, may also be a cofactor. Again, a direct role for HTLV-III must also be considered, since this class of virus clearly has lymphomagnetic potential, as documented by HTLV-I in adult T-cell leukemia/lymphoma (ATL). Molecular analysis with cloned HTLV-III probes should help to clarify these relationships.

Among homosexuals, squamous cell carcinoma of the tongue and cloacogenic carcinoma of the rectum have also been reported. However, this risk antedated the AIDS epidemic, and the frequency of occurrence of these forms of cancers has not increased detectably during the course of the epidemic.[62]

HTLV-III IN AIDS

The transmissible agent responsible for AIDS-associated immunoablation has only recently been isolated.[4] This agent, called HTLV-III, is a cytopathic member of a newly discovered family of human lymphotropic retroviruses previously most strongly linked to a form of aggressive, mature T-cell leukemia termed adult T-cell leukemia/lymphoma.[74] Contrary to the lymphoproliferative pattern of infection associated with HTLV-I and HTLV-II, HTLV-III appears to cause AIDS-associated immunosuppression by lysing the infected target OKT-4 "helper cell" population.[64]

Prior to this discovery, a member of the HTLV family of viruses was postulated as the etiologic agent because of animal models, where altered immunity and immunoablation are an outcome of retrovirus infection.[75] Furthermore, experiments employing a serologic assay for the HTLV-I membrane antigen (MA) documented that AIDS patients had low titer antibodies, cross-reactive at the threshold of assay sensitivity, in 30% to 50% of AIDS cases, compared to 1% of controls.[76] This finding was supported by similar results in AIDS at-risk hemophilia patients and a high concordance of HTLV-I MA antibodies in transfusion-associated AIDS cases.[77,78] It is now clear, using the Western blotting technique with lysates of HTLV-I, HTLV-II, and HTLV-III, that the major envelope gene product of HTLV-III shares distinct antigenic cross-reactivity with both HTLV-I and HTLV-II, confirming that the three known types from this family are immunologically related.[79]

The breakthrough that led to the discovery of HTLV-III resulted from the application of techniques developed in the isolation of HTLV-I and HTLV-II and the identification of an immortalized T-cell line resistant to the cytopathic effects of the virus, which allowed for the reproducible isolation of HTLV-III from various patient groups with AIDS, pre-AIDS, or at risk for AIDS (Table 53-3).[64] The morphology of this agent resembles that of isolates from France, termed LAV and IDAV, and, despite some controversy concerning antigenic cross-reactivity of these isolates to previous HTLV-I and HTLV-II isolates, it is likely that these viruses are identical.[80,81]

The evidence that HTLV-III is the etiologic agent of AIDS comes from the fact that HTLV-III has been routinely isolated and serologically detected from AIDS patients and various patients from pre-AIDS and at-risk groups (Table 53-3).[4,65] Overall, these data provide, strong evidence that HTLV-III is intimately linked to AIDS as the etiologic agent. Further studies are now underway to forge this link in prospectively defined cohorts, where HTLV-III seroconversion is expected to result in clinical AIDS in some proportion of exposed individuals.[66] Given the possibility that substantial numbers of people from certain high-risk groups are likely to have been exposed, determination of the natural history of HTLV-III infection is of critical importance. In particular, cofactors which modify risk for AIDS in the exposed group are likely

TABLE 53-3. HTLV-III and AIDS

DIAGNOSIS	HTLV-III ISOLATION	HTLV-III SEROLOGY
Pre-AIDS	18/21 (85.7%)	11/14 (78.6%)
AIDS	26/72 (36%)	43/49 (87.8%)
Clinically normal AIDS contacts	3/4 (75%)	N/A
Clinically normal at risk for AIDS	1/22 (4.5%)	6/17 (35%)
Clinically normal contacts	0/115 (0%)	1/164 (0.6%)

(Adapted from Gallo RC, Salahuddin SZ, Popvic M et al: Frequent detection and isolation of cytopathic retroviruses [HTLV-III] from patients with AIDS and at risk for AIDS. Science 224:500–503, 1984; and Sarngadharan MG, Popovic M, Bruch L et al: Antibodies reactive with human T-lymphotropic retroviruses [HTLV-III] in the serum of patients with AIDS. Science 224:506–508, 1984).

to be identified with potential for modifying disease outcome. Given the lessons gained in studies of other immunosuppressed groups at risk for lymphoid malignancy, one such cofactor is likely to be chronic antigenic stimulation, a feature prominent in homosexual and hemophiliac AIDS at-risk groups, where large numbers of clinically healthy adults may harbor subclinical immunologic defects that may predispose them to cancer.

Finally, the lack of a general diathesis of malignancy, the lack of any excesses of some of the more common tumors (with the exception of skin cancer, as noted), and the restriction of large excess risks of rare tumor types, all lead to a relatively low absolute risk of malignancy (with the exception of Kaposi's sarcoma in AIDS patients), even among some of the most profoundly immune deficient populations. For example, the highest quantified risks in renal transplant patients are on the order of 2 to 6 non-Hodgkin's lymphoma cases per 1000 patients per year. This observatioin has considerable practical significance in terms of counseling these patients, although similar quantification of the malignancy risk in AIDS is needed. In addition, it indicates that either the immune system is less involved in the carcinogenic process than is widely believed or the human organism has a remarkable compensatory capacity, enabling its adjustment to potentially hazardous alterations of the immune system.

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